ABSTRACT

THESIS: MITOCHONDRIAL DYSFUNCTION INDUCED BY mAB10F5 IS ATTENUATED BY CO-TREATMENT WITH MG53.

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PURPOSE: Rheumatic heart disease (RHD) is an autoimmune disorder triggered by prolonged *Streptococcus pyogenes* infections. MAb10F5 is an autoimmune antibody produced in response to *S. pyogenes* infections and contributes to progression of RHD. The complexity of molecular mimicry seen in *S. pyogenes* has made understanding mAb10F5 pathogenic mechanisms a great challenge, resulting in limited to no treatment options for RHD patients. Recently, our lab found elevated levels of anti-phospholipid antibodies post administration of mAb10F5 epitope in Lewis rats, suggesting that mAb10F5 is an anti-phospholipid antibody. Due to the significant function and abundance of the phospholipid cardiolipin in the mitochondrial membrane, we are interested in mitochondrial function in presence of mAb10F5 within human valvular interstitial cells. A second component of this study involves Mitsugumin-53 (MG53), a TRIM family protein. MG53 has been investigated for its therapeutic potential in a variety of disease models, including cardiovascular disease. Very recently, MG53 was found to bind cardiolipin within mitochondria of cardiovascular cells under stressed conditions, leading to inhibition of cellular apoptosis and initiating membrane repair. Measuring ROS production and ATP availability, together, will shed light on mitochondrial function of HVIC cells after treatment with mAb10F5, MG53, and co-treatment including both. Results from this study have the potential to impact current understanding of the role mAb10F5 has in RHD pathogenesis and could potentially lead to new treatments that are less invasive than surgical procedures. **METHODS:** A novel approach to studying the effects of mAb10F5 and MG53 on mitochondrial function in human valvular interstitial cardiac cells (HVIC) was carried out by (1) measuring reactive oxygen (ROS) production and (2) adenosine triphosphate (ATP) availability. A mitoSOX assay assessed ROS production, while a luciferase ATP assay assessed ATP availability. **RESULTS:** The luciferase ATP assay showed that mAb10F5 treated HVIC resulted in significantly lower ATP concentrations than other groups. 3-Point mitoSOX Analysis showed marked increase in ROS production in mAb10F5 groups. **CONCLUSION:** The results of this study suggest that mAb10F5 may contribute to pathogenic mechanisms of diseases, such as Rheumatic Heart Disease, through disrupting mitochondrial function. Our study also suggests that MG53 may confer protective effects against mAb10F5 induced injury.